REMARKS

Claims 1 to 50 are pending. Claims 1, 10, 11, 12, 16, 25, and 28 have been amended to indicate that the group of organic compounds employed in the present invention are subjected to random chemical processes. Support for the amendment can be found throughout the specification, for example, at page 10, lines 14-17, which indicates that the original substrates are subjected to random chemistry processes to generate a greater diversity from which a compound having a desired property may be detected for further characterization. The amendment also is supported, for example, at page 16, line 26, to page 27, line 3, which indicates that randomly chosen antibody molecules are able to catalyze a randomly chosen reaction with substrates. No new matter has been added by this amendment. Therefore, entry of the amendment is respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 13 to 15 and 46 to 48 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time of filing. Applicants understand that this rejection is based upon the written description requirement of 35 U.S.C. § 112, first paragraph, whose function is to convey to those of ordinary skill in the art that applicants were in possession of the claimed

subject matter at the time of filing of the application. This function can be accomplished in any manner that allows the skilled artisan to recognize that applicant invented the claimed subject matter, *In re Wertheim*, 191 U.S.P.Q. 90 (CCPA 1976).

The Office Action concedes that the specification describes a mathematical and theoretical calculation of how to obtain 1 million and 100 million different enzymes, but alleges that the specification fails to show possession of 10,000 to 100,000,000 different enzymes in real practice.

For the reasons that follow, Applicants respectfully traverse this rejection. The present invention is directed to the production of an organic molecule having a desired property through the random reaction of a mixture of at least 10 different organic molecules. In one embodiment, enzymes which cause the chemical reaction are added to the reaction mixture. The specification specifically states on page 17, lines 17-19, that "a diversity of 1,000 organic molecules is incubated with a diversity of 1,000,000 antibody molecules" (emphasis added). The specification further discusses the use of an enzyme library containing 500,000 candidate enzymes (page 45, lines 24-31) or 250,000 candidate enzymes (page 46, lines 10-11).

At page 16, lines 23-26, the specification recites that "as a non-limiting example to illustrate the general character of the phase transition in catalyzed reaction graphs, a set of 100,000,000 cloned human antibody molecules is used as the set of candidate enzymes (emphasis added). The specification further

discloses at page 20, lines 5-8, that "it is further well known in the art that a cloned high diversity library (10^8 or more) of antibody molecules can be and has been created in a variety of ways. Thus, such antibody libraries are a non-limiting example of a high diversity set of candidate enzymes."

The specification discloses production of a library of 100,000,000 candidate enzymes from a library of 1,000,000 candidate enzymes and, thus, describes how to produce larger libraries of enzymes from smaller libraries of enzymes (page 22, lines 14-18). The specification also discloses at page 51, lines 3-9, that desired product concentrations and catalyzed reactions can be achieved with diversities of 10^4 (10,000) in both the DNA and polypeptide libraries and that diversities of 10^5 to 10^6 (100,000 to 1,000,000) in both the substrate and catalyst library are needed for unimolecular reactions such as cleavage or phosphorylation. At page 56, lines 12-13, the specification discloses the use of a library containing 10,000 polypeptides (enzymes).

Thus, the specification clearly teaches the public that Applicants were in possession of enzyme libraries having from 10,000 to 100,000,000 molecules. Further, libraries of enzymes having 10,000 members, 1,000,000 members, and 100,000,000 and their use in the process of the present invention are specifically recited in the specification. Thus, written description of claims 13 to 15 and 46 to 48 is explicitly provided in the specification.

For these reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 13 to 15 and 46 to 48 under 35 U.S.C. § 112, first paragraph, for allegedly lacking adequate written description.

Rejections under 35 U.S.C. § 102(e)

Claims 1 to 12, 16 to 22, and 25 to 28 stand rejected under 35 U.S.C. § 102(e) as anticipated by Civelli et al. (U.S. Patent 5,441,883). The Office Action asserts that Civelli et al. describes a method for the production of an organic molecule having a desired property which involves inherently providing a reaction mixture with at least 10-100 different organic molecules in solution in the same reaction container and causing at least one chemical reaction to take place with at least some of the different organic molecules in the reaction mixture to create a reaction mixture having one or more organic molecules different from the organic molecules in the starting mixture, followed by repetition of the reaction step to produce a final reaction mixture. The final reaction mixture is then screened for the presence of the organic molecule having the desired property.

Applicants respectfully traverse this rejection for the following reasons. The claims as amended are directed to random chemical reactions with at least one of the group of organic molecules present in the solution in the reaction chamber. Civelli et al. does not teach the random reactions as claimed by the invention. Example 6 of the reference has been cited in support of the rejection. However, the series of reactions in

Example 6 are not random chemical reactions. Rather, the reactions in Civelli et al. are template directed reactions. Since none of the reactions in Civelli et al. are random chemical reactions, the reference does not teach each and every limitation of the claims and, therefore, cannot anticipate the claims.

For these reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1 to 12, 16 to 22, and 25 to 28 under 35 U.S.C. § 102 over Civelli et al.

Claims 36 to 45 and 49 to 50 stand rejected under 35 U.S.C. § 102(e) as anticipated by Iacobucci et al. (U.S. Patent 5,350,681). The Office Action asserts that Iacobucci et al. describes a method in which a group of different substrates is reacted with a group of different enzymes. The Action further asserts that the group of different substrates all share a common core structure and that Iacobucci et al. inherently includes a method where the group of different substrates contain an unlimited number of different organic molecules.

Applicants respectfully traverse this rejection for the following reasons. Iacobucci et al. does not describe a method in which a group of different substrates is reacted with a group of different enzymes. Instead, Iacobucci et al. describes a method for the enzymatic synthesis of a single compound, a peptide, from two single reactants. One of the reactants is a single protected peptide having a C-terminal carboxylate group or

a single protected N-acyl amino acid having an alpha carboxylate group. The other reactant is a single protected peptide having an N-terminal amino group or a protected amino acid having an alpha ammonium group. The two single compounds are reacted in the presence of a condensation enzyme, allowing condensation of the carboxylate group and the amine group to for a protected peptide. Nowhere does Iacobucci et al. describe the reaction of two separate groups of compounds.

The Office Action cites several passages in the reference to support the rejection. The first such passage is the Abstract. However, the abstract describes reaction of two individual compound to form a single product. Nothing in the abstract describes the reaction of two "groups" of reactants.

Examples 11 and 12 are also cited in support of the proposition that Iacobucci et al. describes the claimed invention. However, Example 11 describes the production of a single compound N-formyl-(β-methyl)-asp-phe-trp-OMe from L-trp-OMe and N-formyl-(β-methyl)-asp-phe-OH. Pepsin in the reaction mixture is the condensation enzyme. It acts as a catalyst and is not incorporated into the final product. As can be seen from the example, the carboxy and amino termini of L-trp-OMe and N-formyl-(β-methyl)-asp-phe-OH react to form an amide bond between tryptophan on the one reactant and phenylalanine on the other. There are no additional reactants present in this example, and only the one product is produced. Thus, Example 11 does not describe the reaction of a group of different substrates with a group of different enzymes.

Similarly, Example 12 of Iacobucci et al. describes the coupling of two single dipeptides, H-gly-phe-OMe and N-CBZ-phe-gly-OH, to form the single product H-CBZ-phe-gly-gly-phe-OMe, which then is hydrolyzed with aminoacylase AMANO to H-CBZ-phe-gly-gly-phe-OH. Papain in the reaction mixture is the condensation enzyme, and 2-mercaptoethanol is a solvent that does not participate in the reaction. There are no additional reactants present in this example, and only the one product is produced. Thus, Example 12 also does not describe the reaction of a group of different substrates with a group of different enzymes.

Figures 12 and 13 also are cited to support the rejection. Figure 12 depicts a comparison of V_{syn} (the average rate of synthesis) and V_{perm} (the average rate of permeation) for the pepsin catalyzed proteosynthesis of N-formyl-(β-methyl)-asp-phe-trp-OMe. Figure 13 describes the papain catalyzed proteosynthesis of N-formyl-(β-methyl)-asp-phe-OMe. It is clear from these Figures that only one compound was tested in each of Examples 11 and 12, Figures 12 and 13, respectively.

The Office Action cites column 4, line 66 to column 5, line 16, to support the assertion that Iacobucci et al. inherently describes a group of different substrates containing an unlimited number of different organic molecules. However, this paragraph simply describes possible protected amino acids and peptides that can be used in the method described in the patent. Nowhere does Iacobucci et al. describe reacting multiple amino acids from this group in a common mixture as recited in the

claims. To the contrary, the description of the methods in Iacobucci et al. provide only for the reaction of two amino acids or two peptides to form a single compound.

Further, the Office Action cites to column 7, lines 14-32, as describing a group of different substrates that all share a common core structure as required by claim 49. However, the compounds listed in this portion of Iacobucci et al. refer to protected intermediate products, peptide methyl esters, and the corresponding hydrolyzed products that can be prepared from the methyl esters. Thus, the reference does not disclose groups of different substrates sharing a common core structure which are reacted with a group of different enzymes having a diversity of catalytic activity as required by the claims and, therefore, cannot anticipate them.

Column 19, lines 5-62, of Iacobucci et al. is cited to show that the desired property is the ability to function as a drug. Column 19 describes uses of β-lactam antibiotics that can be prepared by the methods of Iacobucci et al. However, these paragraphs do not describe isolation of the drug from a mixture of organic molecules as required by claim 36 nor do they describe determination of the structure or functional properties of the drug as required by claim 37. Thus, the reference does not describe each and every limitation of the claims.

For these reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 36 to 45 and 49 to 50 under 35 U.S.C. § 102 over Iacobucci et al.

Rejections under 35 U.S.C. § 103

Claims 1 to 12 and 16 to 24 stand rejected under 35 U.S.C. § 103(a) over Civelli et al., U.S. Patent 5,441,883, in view of Furka et al., Int. J. Pep. Protein Res., 37: 487-93 (1991). The Office Action asserts that Civelli et al. describes the methods of claims 1 to 12 and 16 to 20 as described in the rejection under 35 U.S.C. § 102, but admits that Civelli et al. does not describe the step of dividing the first reaction mixture into at least two subgroups, each containing less than all of the different organic molecules in the starting group. However, the Office Action asserts that Furka et al. describes the step of dividing the reaction mixture with different molecules into at least two subgroups, each containing less than all of the different organic molecules in the starting group. The Office Action alleges that it would have been obvious to divide the reaction mixture of Civelli et al. into at least two subgroups as described by Furka et al.

Applicants traverse this rejection for the following reasons. As discussed above in response to the rejection under 35 U.S.C. § 102, Civelli et al. does not describe random reactions with a group of organic molecules. Therefore, the claims are not obvious over Civelli et al. alone.

Furka et al. describes solid phase synthesis of peptide mixtures. The syntheses described in Furka et al. are not random. Nothing in Furka et al. overcomes the deficiency of

Civelli et al. Thus, the combination of references also does not obviate the claims.

For these reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1 to 12 and 16 to 20 under 35 U.S.C. § 103 over Civelli et al. in view of Furka et al.

Claims 29 to 35 stand rejected under 35 U.S.C. § 103(a) over Shen et al., U.S. Patent 3,932,498, in view of Fodor et al., Science, 251: 767-73 (1991). The Office Action asserts that Shen et al. teaches a method for the production and generation for characterization of an organic molecule having a desired property which involves reacting a group of different acid substrates with a dehydrating agent under suitable conditions to yield a first reaction mixture followed by reaction of the first reaction mixture with a reducing agent to yield a second reaction mixture, which is then reacted with an oxidizing agent to provide a third reaction mixture that is condensed to provide a fourth reaction mixture.

The Action concedes that Shen et al. do not describe a method of exposing an organic reaction mixture to light having a wavelength of about 220 nm to 600 nm to produce one or more molecules different from the substrates and agents, but alleges that Fodor et al. describes such a method. The Action further concedes that Shen et al. do not teach a method of screening the exposed reaction mixture for the presence of the organic molecule and isolating the molecule having the desired property from the

reaction mixture, but similarly alleges that Fodor et al. describe a method of screening the reaction mixture for the presence of the organic molecule and isolating a molecule having the desired property form the reaction mixture.

The Office Action asserts that it would have been prima facie obvious to combine and substitute the steps of exposing an organic reaction mixture to light with a wavelength of about 22 nm to 600 nm to produce one or more organic molecules different from the substrates and agents of Fodor et al. in the method for production of an organic molecule having a desired property of Shen et al. since Fodor et al. states that high-density arrays formed by light-directed synthesis are potentially rich sources of chemical diversity for discovering new ligands that bind to biological receptors and for elucidating principles governing molecular interactions.

Applicants respectfully traverse this rejection for the following reasons. Shen et al. does not describe a method in which a group of different substrates, selected from acids, amines, alcohols, and unsaturated compounds, are reacted to yield a first reaction mixture, followed by reduction with a reducing agent, oxidation with an oxidizing agent, and condensation to produce a reaction mixture. Rather, Shen et al. describes reaction of a single compound to produce a single compound.

The Office Action cites the reaction scheme depicted in column 8 and the corresponding description in Column 5 of Shen et al. to support the rejection. It appears that the Office's

position is that the generic structures provided in the reaction scheme indicate reaction of a mixture of compounds. However, use of a generic formula in patent applications is not generally considered to indicate a mixture of reactants unless the specification makes clear that a mixture is intended. Here, consideration of the reference as a whole makes it clear that reaction of a mixture of starting materials is not intended.

Nowhere, does the description in the reference indicate that a mixture of compounds are reacted. In fact, at column 4, lines 19-33, Shen et al. describes the method of their invention in general terms. The process is described as employing a β-aryl propionic acid as the starting material. Although many different β-aryl propionic acids can be used as starting materials, they are not described as being used simultaneously in a mixture. Several alternative methods for producing the starting material are provided, however in each case the specification refers to the components of each step in the singular. For example,

> a substituted benzaldehyde may be condensed with a substituted acetic ester in a Claisen Reaction or with an α-halogenated propionic ester in a Reformatsky Reaction. The resulting unsaturated ester is reduced and hydrolyzed to give the benzyl propionic acid starting material (lines 19-23, emphasis added).

The text cited in column 5 similarly describes reaction of a single starting material in any of a series of alternative reactions to provide a single final product. This is illustrated by the examples of Shen et al. In Example 1, methyl-5-fluoro-2-methylindenyl-3-acetate is reacted with lithium aluminum hydride in an ether solvent. Thus, only a single compound, methyl-5-fluoro-2-methylindenyl-3-acetate, not a mixture, is reacted. The intermediate product is then reacted with methanol and water to produce the corresponding single alcohol, 5-fluoro-2-methylindenyl-3-(β-ethanol). This single alcohol is then reacted with chromium trioxide-bis-pyridyl complex in a methylene chloride solvent to provide the corresponding single aldehyde, 5-fluoro-2-methylindenyl-3-acetaldehyde. The aldehyde is then reacted with methyl bromoacetate, in the presence of zinc dust and crystal iodine in a benzene solvent to provide the ester methyl 5-fluoro-2-methyl-3-indenylγ-(β-hydroxybutyrate). At this point, the single ester is hydrolyzed to the corresponding acid, which is formed as a racemate of cis-, trans-enantiomers, each of which can then be isolated.

Thus, Shen et al. does not describe a method for the production of an organic molecule, having a desired property, through a series of specific reactions on a group of different substrates. Fodor et al. describes solid phase photolithography. Nothing in Fodor et al. overcomes this deficiency. Therefore, the claims are not obvious over the combination of references.

For these reasons, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103 over Shen et al. in view of Fodor et al.

CONCLUSION

In light of the Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned agent or Cathryn Campbell.

Respectfully submitted,

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